LONGTERM FOLLOW-UP OF PATIENTS IN CSP 298 "TREATMENT OF PATIENTS WITH ACQUIRED DEFICIENCY SYNDROME (AIDS) AND AIDS RELATED COMPLEX

ANNUAL REPORT

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13. ABSTRACT *(Maximum 200 words)*

In order to determine whether there is a long-term benefit to initial versus delayed treatment with AZT, a long-term follow-up study is being conducted for patients enrolled in a USAMRDC funded, randomized trial of early versus later zidovudine (AZT) therapy in patients with symptomatic HIV infection and CD4 counts between 200 and 500 cells/cmm. At the present time, the study demonstates no survival benefits, no reduction in the number or rate of progression to AIDS, no improvements in the quality of life in one or the other treatment arm, and some emergence of low level resistance in patients treated with AZT for more than one year. These studies are continuing with approximately 73% of the original study population.

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M.S. Simberkoff by JDH
Principal Investigator's Signature Date

ANNUAL REPORT TO ARMY
April 30, 1992

I. Introduction

This is the first annual report for the extended follow-up of patients originally enrolled in the VA CSP Study No. 298. The original study was a 4-year, double-blind, placebo-controlled study of the efficacy and safety of azidothymidine (AZT: 250 mg q 4 hr, p.o.) for patients with symptomatic HIV infection and CD4 counts between 200 and 500 cells/mm^3. In that study we compared the benefits and liabilities of initiating AZT early (i.e., at study enrollment) versus initiating it late (i.e., when AIDS occurred or CD4 counts declined to < 200 cells/mm^3). That study ended in January 1991, finding that early AZT therapy delays the progression to AIDS but does not give a concomitant increase in survival time [1].

The present study is a 3-year extended follow-up of the patients who survived the original study. Its goals are to assess early versus late AZT therapy in terms of long-term morbidity, toxicity, and drug resistance. For this study, the dosage of AZT is 500 mg daily, which accords with the dosage now recommended by the manufacturer and the FDA.

II. Study results

The results reported here are based on data collected as of January 17, 1992. More than 70% of the 295 patients who were alive at the end of Part I of the study agreed to participate in Part II. Of these, almost 90% take AZT, and 12% some other anti-retroviral agent (ddI, ddC). Ten percent are, or have been, enrolled in other studies. Table 1 shows the status of patients by treatment group, and Table 2 shows their status by hospital.

Unfortunately, many of the patients, as we follow them for longer periods of time, are becoming sicker. This has resulted in an increased death rate in the last year, although not an increased rate of progression to AIDS.

Survival. Since January 19, 1991, when Part II of the study began, there have been 18 deaths in the early-therapy group and 18 deaths in the late-therapy group. (The cumulative deaths for Part I and Part II are 41 in the early-therapy group and 38 in the late-therapy group, which is not a significant difference.) After an AIDS diagnosis, the median survival is 17.3 months for the late-therapy group and 13.7 months for the early-therapy group ($p = 0.93$), as shown in Figure 1.

Progressions. During Part II, there have been 9 progressions to AIDS in the early-therapy group and 14 progressions in the late-therapy group (the cumulative progressions for Part I and Part II are 37 and 61 for the early- and late-therapy groups, respectively;

p = 0.009). Table 3 shows these progressions according to treatment group as well as according to CD4 stratum at study entry, race, and history of i.v. drug use. The early-therapy group continues to have a substantial advantage over the late-therapy group by experiencing a delay in the onset of AIDS. In the various subgroups shown in Table 3, the relationships are much the same as they were at the end of Part I, but with increased numbers of events more of these are significant. The relative risks, reported as early compared to late therapy, remain substantially the same as they did at the end of Part I. The confidence intervals, however, are shorter.

Viral Resistance. Peripheral blood mononuclear cells (PBMCs) from 393 samples, and the virus recovered from 286 of them, have been shipped to Walter Reed in two shipments. A fourth group of specimens is currently being readied for shipment.

We are continuing to work on a case-control study of virus resistance in collaboration with Burroughs Wellcome. We have identified 45 pairs of patients, matched by their CD4 count and length of exposure to AZT, in whom the case has progressed to AIDS or has had a sustained fall in CD4 count and the control has not. Currently 17 pairs have adequate information for a comparison. Eleven of the pairs showed no difference. In the remaining 6 pairs the case had resistant virus and the control had sensitive virus (p = 0.04) [2].

Toxicity. Reports of toxicity remain minimal, especially with the lower dosage now being used. Table 4 shows the toxicity reports using the ECOG Toxicity Scale for the study overall (Part A) as well as the reports that occurred before patients were switched to open-label AZT (Part B). During most of Part I of the study, patients were switched to open-label only after they had progressed to AIDS or their CD4 counts had declined to below 200 cells/mm^3. Late in Part I, however, patients on blinded drug were given the option of switching to AZT [3], which some of them did. In Part II, all patients receive open-label.

Other measures. We are developing a manuscript on the quality of our patients' lives in Part I. Analyses are not complete; however, we are looking at variables such as weight change, hospitalizations and days of limited activity, and the Sickness Impact Profile. In addition, for neuropsychological information, we are collecting data from the Trails A and Trails B tests, which we began administering at the beginning of Part II. Our neuropsychological consultant is of the opinion that these tests, in particular the Trails B, may discriminate between the two treatments over time.

Publications. The main findings from Part I were published in *The New England Journal of Medicine* on February 13, 1992 [1]. Also, we have submitted a paper on the "Ethical Dilemmas in Continuing a Zidovudire Trial After Early Termination of Similar Studies," which

has been accepted by *Controlled Clinical Trials* [3]. We presented abstracts at the latest meetings of the American Federation for Clinical Research [4, 5] and the Interscience Conference on Antimicrobial Agents and Chemotherapy [6]. We have submitted abstracts to the upcoming International AIDS meeting, which have been accepted [2, 7], to the Society of General Internal Medicine [8], and to the upcoming Interscience Conference on Antimicrobial Agents and Chemotherapy [9]. Other manuscripts based on the results of Part I are in preparation.

Administrative. The annual meeting of the study group was held in February in Denver, CO. The Cochairmen and Biostatistician for the study felt that the meeting was very informative and, in addition, productive in stimulating ideas for additional data analyses and, consequently, new manuscripts. Also in February, the Data Monitoring Board reviewed the data. The comments of the Board are enclosed as Appendix A.

III. Conclusion

Part II of the study is continuing well. Most of the original patients are being followed on a regular basis. For those who are not followed in our clinics, we regularly check the VA BIRLS (Benefits and Information Retrieval and Location Service) for their deaths. Also we continue to attempt locating patients who are lost to the study and to keep abreast of their medical progress.

TABLE 1

PATIENT STATUS BY TREATMENT GROUP

	NUMBER OF PATIENTS	EARLY	LATE	TOTAL
	Enrolled	170	168	338
Part I	Died	23	20	43
	Progressed	28	48	76
Part II	With consent forms	95	109	204
	Died	18	18	36
	Progressed	9	13	22
	On AZT	90	97	187
	On other HIV retroviral therapy	12	13	25
	On other HIV therapy	4	3	7
	With samples for virus recovery	98	112	210
	On other studies	6	16	22
Overall	Died	41	38	79
	Progressed	37	61	99

TABLE 2

PATIENT STATUS BY HOSPITAL

	MI	HO	NY	SF	DC	LA	WR
Number of patients	51	44	56	76	30	55	24
Part I							
Number died	8	7	10	7	1	10	0
Number progressed	11	12	18	17	1	16	1
Part II							
Number with consent forms	39	26	31	53	9	37	9
Number died	6	6	4	10	1	9	0
(Consented)	(5)	(0)	(1)	(7)	(0)	(5)	(0)
Number progressed	8	1	1	6	1	4	1
Number on AZT	28	23	31	43	13	40	9
Number on other HIV therapy	11	2	1	9	1	8	0
Number with samples for virus recovery	38	26	31	52	14	39	10
Number on other studies	10	0	2	6	0	4	0

TABLE 3

SUMMARY OF CLINICAL OUTCOMES - PROGRESSION TO AIDS

		Early N	Early (%)	Late N	Late (%)	P value	Relative Risk	95% Confidence Interval
Overall		37	(22)	61	(36)	0.009	0.58	(0.39 - 0.87)
Low Stratum		13	(28)	23	(51)	0.054	0.51	(0.25 - 1.01)
High Stratum		24	(19)	38	(31)	0.060	0.61	(0.37 - 1.03)
White		21	(20)	45	(41)	0.002	0.44	(0.26 - 0.74)
	Low	7	(21)	18	(56)	0.005		
	High	14	(19)	27	(34)	0.064		
Black/Hispanic		16	(25)	16	(28)	0.877	1.02	(0.51 - 2.05)
	Low	6	(50)	5	(38)	0.273		
	High	10	(20)	11	(25)	0.589		
Non-IVDU		26	(21)	48	(37)	0.010	0.54	(0.33 - 0.86)
	Low	8	(24)	19	(53)	0.028		
	High	18	(20)	29	(31)	0.099		
IVDU		11	(23)	13	(34)	0.498	0.74	(0.33 - 1.65)
	Low	5	(42)	4	(44)	0.865		
	High	6	(17)	9	(31)	0.373		
Low	White	7	(21)	18	(56)	0.005		
	Blk/Hisp	6	(50)	5	(38)	0.273		
	Non-IVDU	8	(24)	19	(53)	0.028		
	IVDU	5	(42)	4	(44)	0.865		
High	White	14	(19)	27	(34)	0.064		
	Blk/Hisp	10	(20)	11	(25)	0.589		
	Non-IVDU	18	(20)	29	(31)	0.099		
	IVDU	6	(17)	9	(31)	0.373		

TABLE 4

TOXICITY (from ECOG Toxicity Scale)

A) **OVERALL**

	EARLY		LATER	
	No. Episodes	Total Duration (months)	No. Episodes	Total Duration (months)
Leukopenia (# pts)	129		135	
Mild	148	833	154	879
Moderate	49	666	51	704
Severe*	31	617	29	498
Mod/Sev	80	1283	80	1102
Thrombocytopenia (# pts)	30		45	
Mild	21	78	40	166
Moderate	11	170	16	190
Severe	4	64	4	35
Mod/Sev	15	234	20	225
Anemia (# pts)	48		40	
Mild	38	129	35	96
Moderate	9	72	20	113
Severe	14	116	9	74
Mod/sev	23	188	29	187
Infection (# pts)	63		68	
Mild	39	233	27	185
Moderate	67	168	59	156
Severe	5	11	15	37
Mod/Sev	72	179	74	193
Hepatic (# pts)	73		65	
Mild	59	274	65	240
Moderate	41	216	24	163
Severe	9	71	8	123
Mod/sev	50	287	32	286
Nausea (# pts)	73		55	
Mild	88	435	54	222
Moderate	15	165	29	121
Severe	0	0	3	41
Mod/Sev	15	165	32	162
Diarrhea (# pts)	71		48	
Mild	94	400	66	830
Moderate	7	63	5	7
Severe	0	0	1	8
Mod/Sev	7	63	6	15

*Severe = Severe or life threatening
Mod/Sev = Moderate, severe, or life threatening

TABLE 4 (continued)

TOXICITY (from ECOG Toxicity Scale)

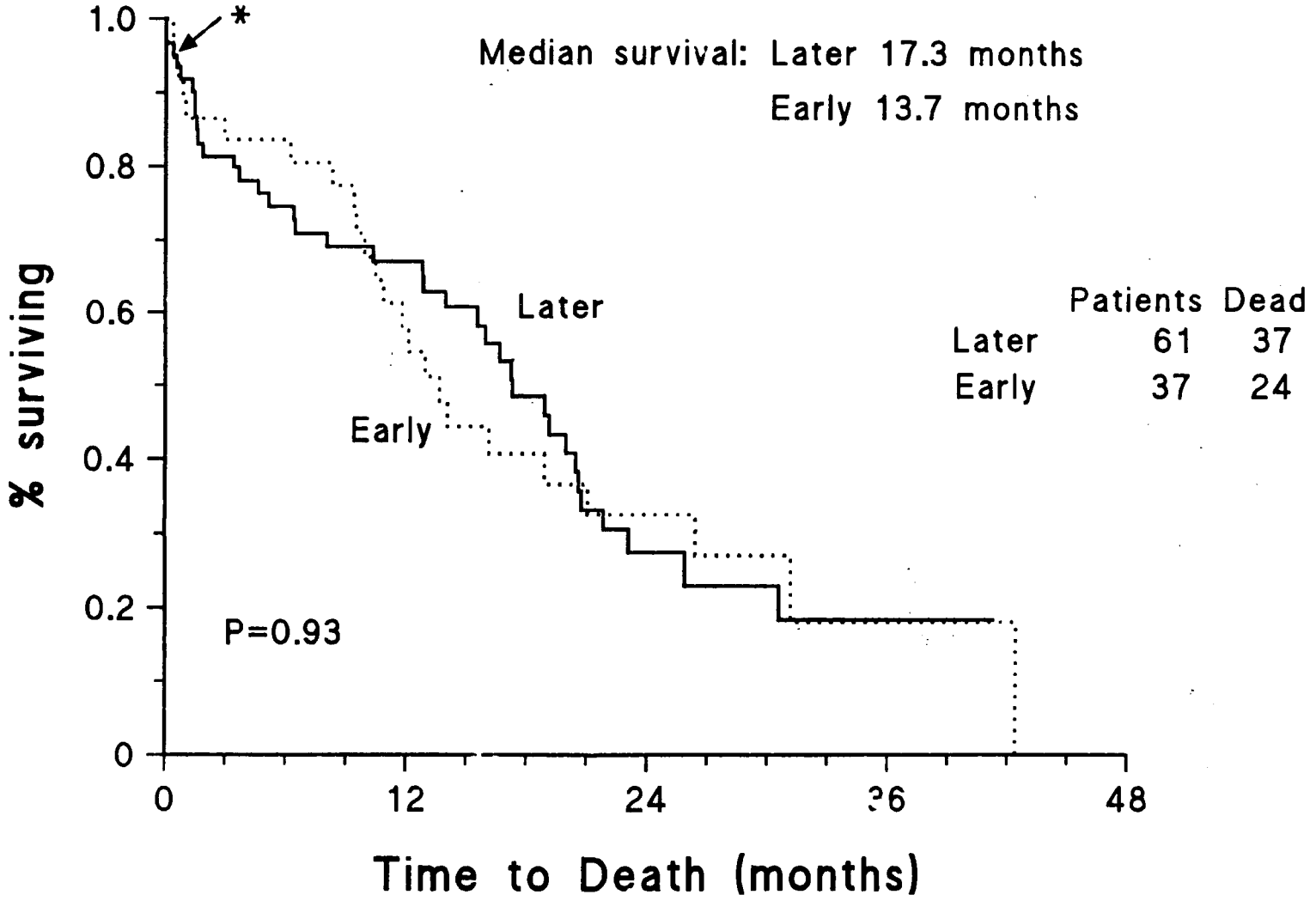
B) **BEFORE OPEN LABEL**

	EARLY		**LATER**	
	No. Episodes	Total Duration (months)	No. Episodes	Total Duration (months)
Leukopenia (# pts)	126		122	
Mild	135	812	136	778
Moderate	45	628	35	559
Severe*	31	617	20	391
Mod/Sev	76	1245	55	950
Thrombocytopenia (# pts)	27		34	
Mild	18	66	27	110
Moderate	9	164	12	155
Severe	4	64	3	28
Mod/Sev	13	228	15	183
Anemia (# pts)	35		16	
Mild	27	97	14	41
Moderate	7	67	8	54
Severe	12	110	1	17
Mod/sev	19	177	9	71
Infection (# pts)	58		57	
Mild	35	222	22	180
Moderate	58	158	47	139
Severe	3	7	9	23
Mod/Sev	61	165	56	162
Hepatic (# pts)	60		48	
Mild	47	234	44	196
Moderate	34	195	19	108
Severe	8	71	6	115
Mod/sev	42	266	25	223
Nausea (# pts)	69		39	
Mild	74	393	41	197
Moderate	14	164	14	60
Severe	0	0	2	36
Mod/Sev	14	164	16	96
Diarrhea (# pts)	62		36	
Mild	76	322	47	756
Moderate	7	63	3	4
Severe	0	0	0	0
Mod/Sev	7	63	3	4

*Severe = Severe or life threatening
Mod/Sev = Moderate or severe or life threatening

FIGURE 1

SURVIVAL AFTER AIDS DIAGNOSIS – (01/17/92)



* includes 2 patients diagnosed at autopsy

References

1. Hamilton JD, Hartigan PM, Simberkoff MS, et al. A controlled trial of early versus late treatment with zidovudine in symptomatic human immunodeficiency virus infection: Results of the Veterans Affairs Cooperative Study. *N Engl J Med* 326:437-443, 1992.

2. St. Clair MH, Hartigan PM, Andrews JC, et al. Matched progressor-nonprogressor study of zidovudine resistance and disease progression. VIII International Conference on AIDS, Amsterdam, The Netherlands, July 19-24, 1992, abstract submitted.

3. Simberkoff MS, Hartigan PM, Hamilton JD, et al. Ethical dilemmas in continuing a zidovudine trial after early termination of similar trials. *Controlled Clinical Trials*, accepted for publication.

4. Simberkoff MS, Hartigan PM, Hamilton JD, et al. Ethical dilemma in continuing a zidovudine-placebo trial in symptomatic HIV infection. American Federation for Clinical Research, Seattle, WA, May 1991. [Also published in *Transactions of the Association of American Physicians* CIV: 92-96, 1991]

5. Hamilton JD, Hartigan PM, Simberkoff MS, et al. Early versus later zidovudine treatment of symptomatic HIV infection: Results of a VA Cooperative Study. American Federation for Clinical Research, Seattle, WA, May 1991.

6. Hamilton JD, Hartigan PM, Simberkoff MS, et al. Early versus later zidovudine therapy for symptomatic HIV infection: Final results of a VA Cooperative Study. 31st Interscience Conference and Antimicrobial Agents and Chemotherapy Meeting in Chicago, IL, October 1991.

7. Simberkoff M, Hartigan P, Hamilton J. Long-term follow-up of VA trial comparing early versus late AZT for symptomatic HIV infection. VIII International Conference on AIDS, Amsterdam, The Netherlands, July 19-24, 1992, abstract submitted.

8. Oddone EZ, Cowper P, Matchar D, Hamilton J, et al. Markov process cost-effectiveness of early versus later zidovudine (AZT) treatment of symptomatic HIV infection. Meeting of the Society of General Internal Medicine, 1992, abstract submitted.

9. Gordin F, Hartigan P, Simberkoff M, et al. Delayed-type hypersensitivity (DTH) reactions are an independent predictor of progression of human immunodeficiency virus (HIV) disease. 32nd Interscience Conference and Antimicrobial Agents and Chemotherapy Meeting, 1992, abstract submitted.

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

DATE: March 25, 1992

FROM: Chair of Data Monitoring Board M. Gail

SUBJECT: Monitoring Report of February 26-27, 1992

TO: Drs. John Hamilton, Michael Simberkoff, Pamela Hartigan and Mrs. Dorothea Collins and to Drs. John Bartlett, Paul Feorino, Robert Redfield and Richard Roberts

The following suggestions were based on comments received through March 18th from the DMB members.

1. If at all possible, the summary patient status report for survival status should include data from all patients, not just patients on part II. In addition to using VA records, it might be helpful to inquire about patient's health by letter or telephone once or twice each year.

2. The case-control study of AZT resistance will determine whether laboratory measures of resistance are associated with increased risk of AIDS. Another question is whether early or late use of AZT promotes more resistance. For this purpose, it might be useful to compare a random sample of "early" patients with a random sample of "later" patients, regardless of AIDS status.

3. In the next report, would it be possible to provide more insight into why survival is as good in the "later AZT" group? One possible mechanism is less low level toxicity (e.g. less nausea and weight loss; see figure on page 67). Another possible mechanism is less AZT resistance. An updated review of causes of death might be useful.

Members of the DMB send their congratulations to all those involved in VA 298. No member of the DMB expressed the need for a conference call.

APPENDIX A

A CONTROLLED TRIAL OF EARLY VERSUS LATE TREATMENT WITH ZIDOVUDINE IN SYMPTOMATIC HUMAN IMMUNODEFICIENCY VIRUS INFECTION

Results of the Veterans Affairs Cooperative Study

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Abstract *Background.* Zidovudine is recommended for asymptomatic and early symptomatic human immunodeficiency virus (HIV) infection. The best time to initiate zidovudine treatment remains uncertain, however, and whether early treatment improves survival has not been established.

Methods. We conducted a multicenter, randomized, double-blind trial that compared early zidovudine therapy (beginning at 1500 mg per day) with late therapy in HIV-infected patients who were symptomatic and had CD4+ counts between 0.2×10^9 and 0.5×10^9 cells per liter (200 to 500 per cubic millimeter) at entry. Those assigned to late therapy initially received placebo and began zidovudine when their CD4+ counts fell below 0.2×10^9 per liter (200 per cubic millimeter) or when the acquired immunodeficiency syndrome (AIDS) developed.

Results. During a mean follow-up period of more than two years, there were 23 deaths in the early-therapy group (n = 170) and 20 deaths in the late-therapy group (n = 168) (P = 0.48; relative risk [late vs. early], 0.81; 95 percent confidence interval, 0.44 to 1.59). In the early-therapy group, 28 patients progressed to AIDS, as compared with 48 in the late-therapy group (P = 0.02; relative risk, 1.76; 95 percent confidence interval, 1.1 to 2.8). Early therapy increased the time until CD4+ counts fell below 0.2×10^9 per liter (200 per cubic millimeter), and it produced more conversions from positive to negative for serum p24 antigen. Early therapy was associated with more anemia, leukopenia, nausea, vomiting, and diarrhea, whereas late therapy was associated with more skin rash.

Conclusions. In symptomatic patients with HIV infection, early treatment with zidovudine delays progression to AIDS, but in this controlled study it did not improve survival, and it was associated with more side effects. (N Engl J Med 1992;326:437-43.)

PLACEBO-controlled trials have demonstrated that zidovudine reduces morbidity and mortality when administered to patients with human immunodeficiency virus (HIV) infection late in the course of their infection,[1] and that this drug also reduces morbidity when administered to symptomatic[2] or asymptomatic patients[3] earlier in the course of infection. The best time to initiate zidovudine therapy remains unknown, however.[1]

We conducted a four-year, multicenter, randomized, double-blind trial to evaluate when to administer zidovudine. Specifically, we wanted to determine the long-term clinical benefits and liabilities of earlier as compared with later therapy in symptomatic patients with HIV infection whose CD4+ counts were between 0.2×10^9 and 0.5×10^9 cells per liter (200 to 500 per cubic millimeter).

From the Department of Veterans Affairs Medical Centers in Baltimore (G.L.D., M.J.E.), Durham, N.C. (J.D.H.), Houston (C.J.L., N.P.W.), Los Angeles (W.L.G., W.A.O.), Miami (G.M.D., N.G.K.), New York (M.S.S., G.R.D., S.B.Z.-P.), San Francisco (P.C.J.), and Washington, D.C. (F.M.G., A.M.L.); the Veterans Affairs Coordinating Centers in West Haven, Conn. (P.M.H.) and Albuquerque, N.M. (P.L.D.); Duke University, Durham, N.C. (K.J.W.); and the Walter Reed Army Hospital, Washington, D.C. (C.A.H., C.N.O.). Address reprint requests to Dr. Hamilton at the Veterans Affairs Medical Center, 508 Fulton St., Durham, NC 27705.

Supported by the Cooperative Studies Program of the Medical Research Service, Department of Veterans Affairs, Central Office, Washington, D.C., and the U.S. Army Medical Research and Development Command.

The opinions and assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

Presented in part at the annual meetings of the American Federation for Clinical Research, Seattle, May 3–6, 1991, and the Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, September 29–October 2, 1991.

*The other members of the study group are listed in the appendix.

METHODS

Patient Population

Patients were selected from seven participating medical centers. To be eligible for the study, they had to have proved HIV infection (as determined by enzyme-linked immunosorbent assay and Western blot test), a peripheral-blood CD4+ lymphocyte concentration of 0.2×10^9 to 0.5×10^9 per liter (200 to 500 per cubic millimeter) as determined by two measurements performed at least two weeks apart, and symptoms or signs of HIV infection. Required symptoms and signs included a history or the presence of thrush, oral hairy leukoplakia, herpes zoster, unintentional weight loss of ≥10 percent of body weight, unexplained persistent diarrhea, fever (temperature, ≥38°C [100.5°F]), night sweats, fatigue, dermatitis, or lymphadenopathy.

Patients were excluded if they had the acquired immunodeficiency syndrome (AIDS) as defined by the Centers for Disease Control (CDC),[3] had received antiretroviral chemotherapy, or had any of the following abnormal laboratory values: a creatinine level of more than 177 μmol per liter (2.0 mg per deciliter), hemoglobin level of less than 5.9 mmol per liter (9.5 g per deciliter), white-cell count below 2.0×10^9 per liter (2000 per cubic millimeter), or granulocyte count below 1.0×10^9 per liter (1000 per cubic millimeter). Patients with unstable disease (defined as active infection or hospitalization within the previous two weeks) and those who were considered unreliable were also excluded.

The protocol and consent forms were approved by the Human

Rights Committee of the Cooperative Studies Program and by the investigational review board at each participating hospital. All the patients gave written informed consent.

Study Design and Treatment Regimens

At enrollment, we stratified patients according to their mean CD4+ cell concentration (stratum 1, 0.200×10^9 to 0.299×10^9 cells per liter [200 to 299 per cubic millimeter]; and stratum 2, 0.300×10^9 to 0.500×10^9 cells per liter [300 to 500 per cubic millimeter]) and randomly assigned them to one of two treatments using a permuted-blocks scheme[6]: zidovudine for the entire study period (early therapy) or placebo followed by zidovudine when the patient's CD4+ concentration fell to less than 0.2×10^9 per liter (200 per cubic millimeter) or when AIDS developed (late therapy). Patients received 250 mg of zidovudine or matching placebo by mouth every four hours (1500 mg per day), a dosage chosen to equal that administered in the initial phase II trial.[7] Patients from both treatment arms who reached a clinical or immunologic end point were switched from blinded therapy to open-label zidovudine therapy at the same dosage (1500 mg per day).

Adverse effects were evaluated according to criteria established by the Eastern Cooperative Oncology Group.[7] When an adverse effect occurred, the study medication was limited to every eight hours (750 mg per day) or stopped, depending on the type and severity of the reaction. When symptoms resolved or laboratory measures improved according to predefined criteria, the study medication was resumed at either the original or the reduced dosage. Additional information on the protocol for adverse effects is available elsewhere.* If the adverse effect did not resolve, the study medication was discontinued.

Modification of the Protocol

In June 1989, after the publication of new guidelines by the CDC, the protocol was revised to allow prophylaxis against *Pneumocystis carinii* pneumonia.[8]

In August 1989, the AIDS Clinical Trials Group announced the termination of its placebo-controlled studies on zidovudine in symptomatic[2] and asymptomatic[3] HIV infection. On the basis of those studies, the Antiviral Advisory Committee of the Food and Drug Administration recommended that zidovudine therapy be initiated for all patients with symptomatic or asymptomatic HIV infection whose CD4+ concentrations were below 0.5×10^9 per liter (500 per cubic millimeter). Our data-monitoring board and its external advisors decided to continue our trial, to inform in writing each study patient of the findings and recommendations of the AIDS Clinical Trials Group and the FDA, and to obtain additional informed consent. Patients who did not wish to continue receiving blinded therapy were offered open-label zidovudine.

Criteria for Response

Death and progression to AIDS[9] were the clinical end points of this study. Our definition of dementia was based on suggested criteria for and staging of the AIDS dementia complex.[9,10] AIDS-related death was defined as death associated with a current AIDS-defining condition. Death with HIV progression was defined as death preceded by AIDS or an HIV-associated illness (e.g., pneumococcal bacteremia and meningitis), increased symptoms, or a decrease in the CD4+ concentration to less than 0.2×10^9 per liter (200 per cubic millimeter). The immunologic end point of the study was a decrease in the CD4+ concentration to less than 0.2×10^9 per liter (200 per cubic millimeter) on two successive measurements performed six or more weeks apart.

Evaluation and Follow-up

Both before and during the study, all the patients were carefully evaluated according to a strict protocol to rule out the presence of an AIDS-defining illness. Additional information on the protocol for screening for AIDS is available elsewhere.* After randomization and the initiation of the blinded study medication, the patients were seen at least monthly for a detailed history, physical examination, and laboratory evaluations. Lymphocyte subgroups and serum p24 antigen levels were measured at months 1, 2, and 4 and at four-month intervals thereafter. Plasma zidovudine concentrations were measured bimonthly at random times within four hours after dosing.

Data Management

Data collected at participating sites were sent to the study co-chairman's office and to the Cooperative Studies Program Coordinating Center for review. Data were keyed in twice for verification and checked routinely for outliers and erroneous values. The study cochairman reviewed the information on all clinical end points (clinical data, pathological and radiologic materials, and the results of laboratory studies) and referred relevant objective data to independent blinded outside consultants.

Special Laboratory Studies

Lymphocyte phenotyping by flow cytometry was performed on peripheral-blood mononuclear cells prepared on a Ficoll–Hypaque gradient or by the whole-blood lysis technique with monoclonal reagents (Becton Dickinson, Mountainside, Calif.).

Serum p24 antigen was measured at a central reference laboratory with an antigen-capture enzyme-linked immunosorbent assay kit (Dupont, Wilmington, Del.; lower limit of sensitivity, 10 pg per milliliter). Plasma zidovudine concentrations were measured at a central reference laboratory by previously described methods.[11]

Statistical Analysis

The comparability of the treatment groups was assessed by a chi-square test or Fisher's exact test for discrete variables and by Student's t-test or the Wilcoxon rank-sum test for continuous variables.[12] Time to toxicity, clinical end points, and immunologic end points were estimated with Kaplan–Meier and proportional-hazards regression methods. Stratified log-rank tests and proportional-hazards models were used to compare treatment groups and to estimate relative risks and confidence intervals, with adjustment for the stratification according to CD4+ cell concentration.[13] Qualitative interactions were tested with the method developed by Gail and Simon.[14] During the study, our data-monitoring board used a modified O'Brien–Fleming boundary to adjust for repeated looks at the data.[15] Here, however, we report classic confidence intervals because they provide a useful summary of the evidence and the amount of information on treatment effect. Throughout, we report the relative risks comparing late treatment with early treatment. Test statistics for comparisons of major end points were regarded as significant if the P value was ≤ 0.05; test statistics for all other end points or subgroups were considered significant at a P level of 0.01. All primary analyses were performed on an intention-to-treat basis, and all P values are two-tailed.

Results

Base-Line Characteristics

A total of 338 patients were randomly assigned to either early therapy (170 patients) or late therapy (168 patients) from January 1987 to January 1990. This number included 11 patients (4 in the early-therapy

*See NAPS document no. 04933 for 16 pages of supplementary material. Order from NAPS c/o Microfiche Publications, P.O. Box 3513, Grand Central Station, New York, NY 10163-3513. Remit in advance (in U.S. funds only) $7.75 for photocopies or $4 for microfiche. Outside the U.S. and Canada, add postage of $4.50 ($1.75 for microfiche postage). There is a $15 invoicing charge for all orders filled before payment.

group and 7 in the late-therapy group) who did not meet the eligibility criteria in minor ways. The exclusion of these 11 patients does not alter the conclusions of the study.

The patients were on average 40 years old. They were predominantly male and non-Hispanic white. Sixty-three percent reported homosexual or bisexual contacts without intravenous drug use, 16 percent reported intravenous drug use, 9 percent were homosexual or bisexual and used intravenous drugs, and 12 percent reported other risk factors. They had an average of three symptoms, a Karnofsky score of 89, and a CD4+ concentration of 0.355×10^9 per liter (355 per cubic millimeter). Nineteen percent of them had p24 antigenemia. There were no statistically significant imbalances between the treatment groups in the distribution of important covariates (Table 1).

Table 1. Base-Line Characteristics of the Study Patients.*

Characteristic	Early Therapy (N = 170)	Late Therapy (N = 168)
Stratum — no. (%) of patients		
1	49 (29)	45 (27)
2	121 (71)	123 (73)
Age at randomization (yr)	40.4 ± 9.4	40.5 ± 10.5
Sex — no. (%) of patients		
Male	169 (99)	166 (99)
Female	1 (1)	2 (1)
Race — no. (%) of patients		
Non-Hispanic white	107 (63)	111 (66)
Black or Hispanic	63 (37)	57 (34)
Risk group — no. (%) of patients		
Homosexual or bisexual contact	103 (61)	110 (65)
Intravenous drug use	30 (18)	24 (14)
Homosexual or bisexual contact and intravenous drug use	17 (10)	14 (8)
Blood transfusion	5 (3)	4 (2)
Heterosexual contact	10 (6)	8 (5)
Unknown	5 (3)	8 (5)
No. of symptoms	3.0 ± 1.9	3.3 ± 1.8
Months since first symptom	36.1 ± 36.5	36.0 ± 37.3
Symptom group — no. (%) of patients		
Night sweats, fever, diarrhea, weight loss	98 (58)	88 (52)
Herpes zoster, thrush, hairy leukoplakia	68 (40)	71 (42)
Dermatitis, fatigue, lymphadenopathy	160 (94)	151 (90)
Karnofsky score	88.6 ± 8.3	88.4 ± 8.8
CD4+ count (/mm^3)	359.7 ± 83.4	348.7 ± 76.9
Serum p24 antigen — no. (%) of patients‡		
Positive	31 (18)	32 (19)
Negative	128 (75)	130 (77)

*Plus-minus values are means ± SD.

‡Only 321 patients were tested for serum p24 antigen. The percentages shown are of the total patient group.

Follow-up and Compliance

The overall mean follow-up periods for the early-therapy and late-therapy groups were 27.2 and 28.2 months, respectively. For blinded therapy, the periods were 14.8 and 13.9 months, respectively ($P = 0.32$). Fifteen patients (nine in the early-therapy group and six in the late-therapy group) were lost to follow-up.

In the early-therapy group, 79 patients switched to open-label zidovudine, 52 because of the protocol and 27 by choice. The 27 who switched by choice did so a mean of 9.6 months before the end of the study, when their median CD4+ count was 0.317×10^9 per liter (317 per cubic millimeter). In the late-therapy group, 121 patients switched to open-label therapy, 82 because of the protocol and 39 by choice. The 39 who switched by choice did so a mean of 10.2 months before the end of the study, when their median CD4+ count was 0.304×10^9 per liter (304 per cubic millimeter).

Of the patients eligible for prophylaxis against *P. carinii* pneumonia, 98 percent of the early-therapy group (46 of 47) received it, as compared with 90 percent of the late-therapy group (54 of 60, $P = 0.14$).

The groups were equally compliant. Sixty-eight and 72 percent of the scheduled visits were made in the early-therapy and late-therapy groups, respectively; pill counts were 94 and 95 percent of expected; and 90 and 92 percent of the plasma zidovudine concentrations were appropriate. During blinded treatment, the early-therapy group had a mean increase of 13.35 fl in mean corpuscular volume, as compared with an increase of 0.086 fl in the group treated later. During open-label treatment, the mean corpuscular volume was on average 14.3 fl above base line.

Clinical End Points

There were 43 deaths, 23 in the early-therapy group and 20 in the late-therapy group ($P = 0.48$; relative risk for late vs. early therapy, 0.81; 95 percent confidence interval, 0.44 to 1.59) (Table 2). Most patients who died had evidence of HIV progression even when death was *not* attributed to AIDS. Only four patients died without evidence of HIV progression; all were in the early-therapy group. The causes were suicide, murder, congestive heart failure, and large-cell undifferentiated carcinoma. AIDS preceded 13 of the 23 deaths in the early-therapy group and all 20 deaths in the late-therapy group. Thus, all 10 of the deaths that

Table 2. Major Clinical End Points.

End Point	Early Therapy	Late Therapy	P Value*	Relative Risk (95% CI†)
	no.			
Death	23	20	0.48	0.81 (0.44–1.59)
AIDS related	13	12		
Non-AIDS related				
With HIV progression	6	8		
Without HIV progression	4	0		
Progression to AIDS	28	48	0.02	1.75 (1.10–2.80)
Kaposi's sarcoma	6	7		
Lymphoma	1	6		
P. carinii pneumonia	11	15		
Other opportunistic infection	8	14		
Dementia	0	6		
Wasting	2	0		
Other illness‡	1	3		
AIDS or death	38	48	0.25	1.29 (0.84–1.97)

*By log-rank test.

†CI denotes confidence interval.

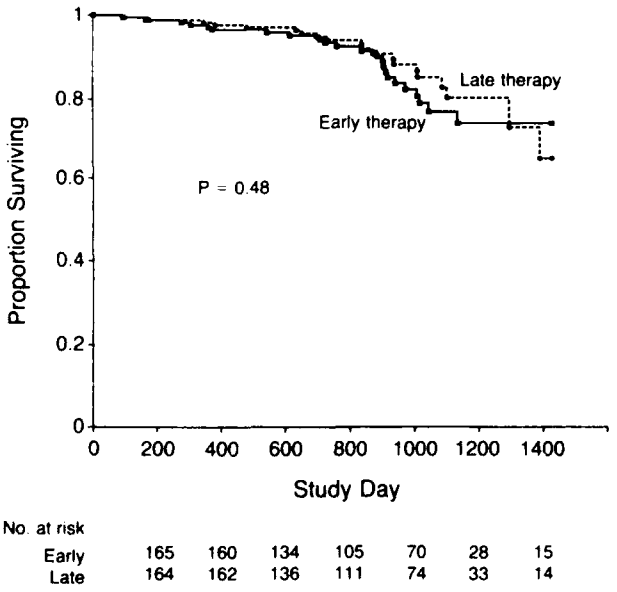
‡The other illness in the early-therapy group was pneumococcal meningitis; in the late-therapy group it was Hodgkin's disease (one patient) and nephrotic syndrome (two patients).

were not preceded by or associated with an AIDS-defining event occurred in the early-therapy group. There was a trend toward earlier non-AIDS-related death in the early-therapy group, which was balanced by earlier AIDS-related deaths in the late-therapy group. Nineteen of the deaths in each group were preceded by at least one CD4+ count of less than 0.2×10^9 per liter (200 per cubic millimeter). The respective survival rates at one, two, and three years were 97, 93, and 77 percent for early therapy and 98, 95, and 83 percent for late therapy (Fig. 1).

The early-therapy group had 28 patients who progressed to AIDS, whereas the late-therapy group had 48 ($P = 0.02$; relative risk, 1.75; 95 percent confidence interval, 1.1 to 2.8) (Table 2). Thirty-nine percent (11 of 28) of those treated early and 31 percent (15 of 48) of those treated later had *P. carinii* pneumonia as their first AIDS-defining condition. The proportion of patients in the early-therapy group who progressed to AIDS and had at least one subsequent AIDS-defining condition was 57 percent (16 of 28), as compared with 42 percent (20 of 48) in the late-therapy group ($P = 0.19$). The respective percentages free of AIDS at one, two, and three years were 93, 84, and 82 percent for early therapy and 91, 79, and 65 percent for late therapy (Fig. 2).

Of the 28 patients in the early-therapy group who progressed to AIDS, 13 (46 percent) subsequently died, as compared with 20 (42 percent) of the 48 patients in the late-therapy group who progressed to AIDS. The median time from the diagnosis of AIDS to death was 16 months in the early-therapy group and 19 months in the late-therapy group ($P = 0.87$).

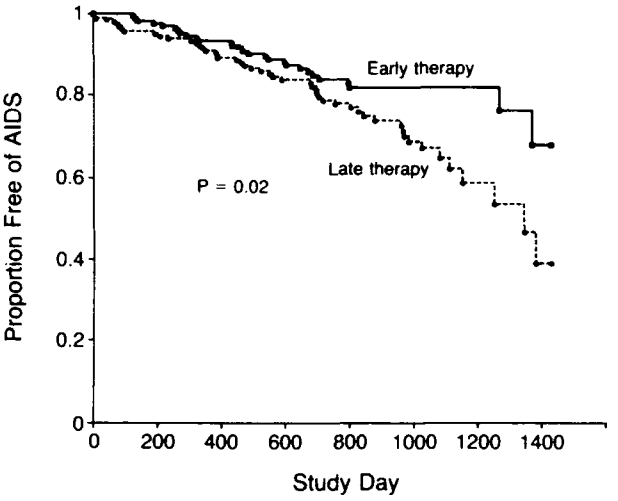
A CD4+ concentration of less than 0.2×10^9 per liter (200 per cubic millimeter) preceded the AIDS-defining events in 17 patients (61 percent) in the early-therapy group and in 35 patients (73 percent) in the late-therapy group. A CD4+ count was obtained within four months before or two weeks after a diagnosis of *P. carinii* pneumonia in 21 of 26 patients (81 percent). In 19 (90 percent) of these patients, the CD4+ concentration was less than 0.2×10^9 per liter (200 per cubic millimeter).



No. at risk

Early	165	160	134	105	70	28	15
Late	164	162	136	111	74	33	14

Figure 1. Estimated Kaplan–Meier Distribution of Time to Death, According to Study Group.



No. at risk

Early	162	152	121	89	58	26	13
Late	159	150	119	93	60	25	9

Figure 2. Estimated Kaplan–Meier Distribution of Time to a Diagnosis of AIDS, According to Study Group.

Proportional-hazards models of the outcomes showed that base-line age and CD4+ count were significantly related to survival, but that Karnofsky score, p24 antigen positivity, symptom count, and medical center were not. By the same models, all these variables were significantly related to progression to AIDS. These effects were independent of treatment.

Clinical End Points within Subgroups

A higher proportion of patients in stratum 1 than in stratum 2 died (24 percent vs. 9 percent), and a higher proportion progressed to AIDS (31 percent vs. 19 percent). Although no treatment difference was significant within strata, the trends for each end point were similar to the overall results (Table 3).

Patients who were positive for p24 antigen at entry were more likely to die or progress to AIDS (18 percent and 33 percent, respectively) than patients who were negative for the antigen (10 percent and 19 percent). Although most treatment comparisons within these subgroups showed no significant differences, early treatment of patients who were negative for p24 antigen delayed the onset of AIDS (Table 3).

Intravenous drug use did not appear to be a major factor in explaining the effects observed. Early therapy significantly delayed progression to AIDS in patients

Table 3. Major Clinical End Points, According to Subgroup.

End Point	Early Therapy		Late Therapy		P Value*	Relative Risk
	No. of Patients	No. of Events	No. of Patients	No. of Events		
Death						
CD4+ cells						
200–299/mm³	46	9	45	11	0.85	1.09
300–500/mm³	124	14	123	9	0.25	0.62
Serum p24 antigen†						
Positive	31	7	32	4	0.35	0.54
Negative	128	13	130	13	0.73	0.91
Intravenous drug use						
Yes	51	7	41	2	0.10	0.37
No	119	16	127	18	0.97	0.96
Race or ethnic group						
Hispanic	15	3	16	0	0.07	—
Black	48	6	41	2	0.15	0.36
Non-Hispanic white	107	14	111	18	0.79	1.12
Progression to AIDS						
CD4+ count						
200–299/mm³	46	9	45	19	0.06	2.13
300–500/mm³	124	19	123	29	0.12	1.59
Serum p24 antigen†						
Positive	31	10	32	11	0.98	0.96
Negative	128	14	130	34	0.01	2.22
Intravenous drug use						
Yes	51	11	41	10	0.99	1.00
No	119	17	127	38	0.01	2.50
Race or ethnic group						
Hispanic	15	4	16	3	0.44	0.66
Black	48	8	41	10	0.70	1.25
Non-Hispanic white	107	16	111	35	0.01	2.33

*By log rank test.
†Only 321 patients were tested for serum p24 antigen.

who did not use intravenous drugs, but no other comparisons produced significant results (Table 3).

The racial and ethnic groups appeared to respond differently to the timing of zidovudine therapy. Fewer minority (black and Hispanic) patients died in the late-therapy group (two deaths) than in the early-therapy group (nine deaths), but the difference was not significant. Among non-Hispanic white patients, early therapy significantly delayed the onset of AIDS but had no effect on survival (Table 3). Minority patients were much more likely than white patients to be intravenous drug users (40 percent vs. 10 percent, respectively). Adjusting the time-to-failure analyses within racial and ethnic groups for intravenous drug use, however, had little impact on either the treatment effect or any possible effect of race or ethnic group.

The only subgroup analysis planned in advance was a comparison within strata. The results of tests for qualitative interaction with treatment were not significant for either death or progression to AIDS in any subgroup.

Immunologic and Virologic Results

As compared with late therapy, early therapy prolonged the time before CD4+ concentrations fell below 0.2×10^9 per liter (200 per cubic millimeter) and were sustained at that level ($P = 0.01$). Changes in CD4+ counts from base-line values showed clear differences between treatment groups over time (Fig. 3A). At 4, 12, and 20 months, respectively, the mean changes from base line were +0.0115, +0.0003, and -0.0355×10^9 cells per liter (+11.5, +0.3, and −35.5 per cubic millimeter) in the early-therapy group, but −0.0086, −0.0487, and -0.0836×10^9 cells per liter (−8.6, −48.7, and −83.6 per cubic millimeter) in the late-therapy group.

At base line, 19.6 percent of the 321 patients tested (95 percent of the total group of 338) were positive for serum p24 antigen. Of these, a higher proportion had converted to seronegative at four months in the early-therapy group than in the late-therapy group (15 of 19 vs. 6 of 17 [79 percent vs. 35 percent]), but the difference was not sustained thereafter (Fig. 3B).

Toxicity of Study Drugs

Leukopenia occurred in 82 percent of the patients receiving early therapy and 77 percent of those receiving late therapy; 20 percent and 16 percent, respectively, had anemia. Fourteen percent and 10 percent, respectively, had severe leukopenia (white-cell count, $<2.0\times10^9$ per liter [2000 per cubic millimeter]; neutrophil count, $<1.0\times10^9$ per liter [1000 per cubic millimeter]); and 5 percent and 2 percent had severe anemia requiring transfusion. Nausea (or vomiting) and diarrhea occurred more frequently in the early-therapy group than in the late-therapy group (40 percent vs. 23 percent, respectively; $P<0.01$). Skin rashes were more common in the late-therapy group (58 percent) than in the early-therapy group (47 percent, $P = 0.03$). The proportions of patients with hemorrhage, fever, infection, peripheral neuropathy, genitourinary symptoms, or symptoms or signs of heart, lung, or liver disease did not differ significantly between the treatment groups.

The dosage of blinded study medication was reduced because of adverse reactions in 64 of the patients assigned to zidovudine (early therapy) and in 29 of those assigned to placebo (late therapy) ($P<0.001$). In 11 of these patients in the early-therapy group and in 2 of those in the late-therapy group, the medication was eventually discontinued ($P<0.01$). During blinded therapy, one or more transfusions (range of units per patient, 2 to 46) were required in 14 patients, 12 in the early-therapy group and 2 in the late-therapy group ($P<0.01$). After patients switched to open-label therapy, 2 additional patients in the early-therapy group and 14 in the late-therapy group required transfusions.

Discussion

The goal of our study was to compare the initiation of zidovudine therapy early in the course of HIV infection, when patients are symptomatic but have CD4+ counts between 0.2×10^9 and 0.5×10^9 per liter (200 and 500 per cubic millimeter), with initiation later on, when the CD4+ count is below 0.2×10^9 per liter (200 per cubic millimeter) or AIDS has developed. After more than two years of follow-up, we

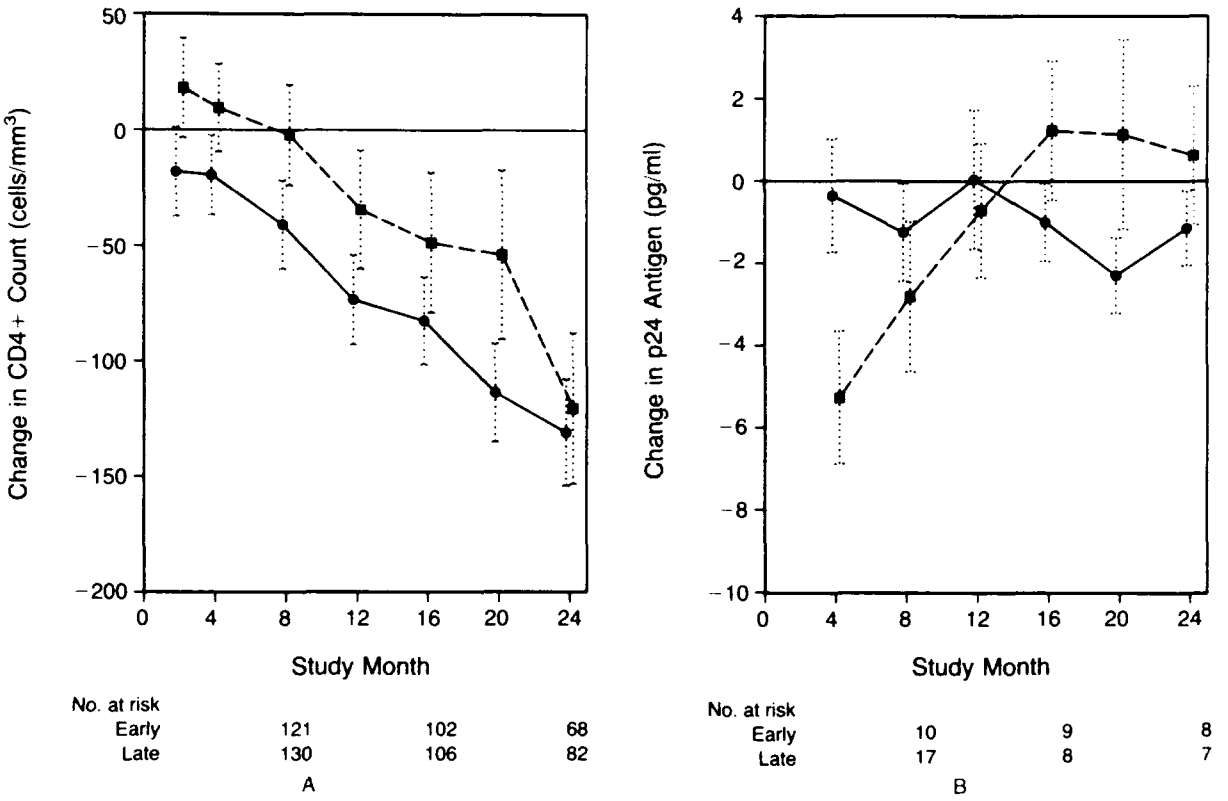


Figure 3. Mean (±SE) Changes from Base Line in CD4+ Counts (Panel A) and Serum p24 Antigen Concentrations (Panel B). Panel A shows results for all the study patients, and Panel B results for patients who were positive for p24 antigen at entry. Squares denote the early-therapy group, and circles the late-therapy group.

found no difference in survival between the two treatment groups. We can exclude any large survival benefit for the early-therapy regimen used in this study, since the confidence intervals indicate that early therapy could provide no more than 1.6 times the benefit of late therapy, but that late therapy could be as much as 2 times more beneficial than early therapy. Excluding data on patients who died without HIV progression did not alter the overall conclusion that there is no survival advantage for either treatment regimen. We believe this conclusion to be generalizable, because our patients were representative of those in our large hospital system and similar to those seen in other public facilities.

In the patients who received early treatment we found a significant reduction in progression to AIDS, a finding that complements those of the placebo-controlled studies conducted by the AIDS Clinical Trials Group in symptomatic[2] and asymptomatic[3] patients. In our study this benefit appeared to be greater in patients with CD4+ counts below 0.3×10^9 per liter (300 per cubic millimeter), in those who had no detectable serum p24 antigen at entry, in those who had not used intravenous drugs, and in non-Hispanic whites.

Early zidovudine therapy slowed the progression to AIDS but did not improve overall survival in our trial. Once AIDS developed in patients receiving early therapy, more of them tended to have multiple AIDS diagnoses, a slightly higher proportion died, and the median survival time was slightly shorter than in similar patients who received late therapy. The time to AIDS-related death or other death was similar in both groups. The 18-month median overall survival after an AIDS-defining diagnosis was similar to that seen in another large series.[16] Furthermore, it must be recognized that we compared earlier with later zidovudine therapy according to a protocol designed so that no patient would continue to receive placebo throughout the follow-up period.

The CD4+ count was consistently higher in the early-therapy group throughout follow-up. This resulted in a significant difference between groups in the proportion of patients who were switched to open-label zidovudine and a sustained difference in the mean CD4+ count through 18 months.

We used a higher dosage of zidovudine than the FDA currently recommends for patients like ours; however, most published randomized studies have had one arm with a dosage similar to ours.[1,3,17] The results of some of these studies have been used to suggest that the benefits of low and high doses are

equivalent and that low doses are preferable because they are less toxic.[3,17] If this is true, our results should be applicable to low-dose therapy if they are not confounded by excess toxicity. Toxic reactions did occur in our patients. They were less frequent, however, than those reported in the study by Richman et al., in which patients received the same dosage as our patients but had more advanced disease.[18] Also, our study included a protocol for lowering the dosage; the number of patients in whom the drug was actually discontinued was small, however. It therefore seems unlikely that adverse effects related to dosage could compromise the conclusions of our study.

The different trends in treatment response that we noted among racial and ethnic groups were the result of unplanned subgroup analyses. The results of unplanned analyses must be regarded with caution and skepticism and do not warrant differential treatment of minority patients. At most, we believe, the results should be used to generate hypotheses for future testing.

Our data raise anew the debate over the best time to initiate zidovudine treatment in patients with symptomatic HIV infection and CD4+ counts higher than 0.2×10^9 per liter (200 per cubic millimeter). On the basis of our data and the reports of Fischl et al.[2] and Volberding et al.,[3] we believe that early zidovudine therapy is an option that warrants consideration in symptomatic or asymptomatic patients with CD4+ counts of less than 0.5×10^9 per liter (500 per cubic millimeter), because initiating therapy at that point clearly delays AIDS-defining events. On the other hand, the long-term effects of zidovudine on the quality of life, cumulative drug toxicity, the development of drug resistance, and the cost of therapy have not been fully clarified. Thus, because of the uncertainty about long-term effects and because no survival benefit has been observed, we also believe that one may consider delaying the initiation of zidovudine therapy in patients whose condition is stable and whose CD4+ counts are between 0.2×10^9 and 0.5×10^9 per liter (200 and 500 per cubic millimeter).

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Appendix

The other members of the Veterans Affairs Cooperative Study Group on AIDS Treatment were as follows:

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References

1. Fischl MA, Richman DD, Grieco MH, et al. The efficacy of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related complex: a double-blind, placebo-controlled trial. N Engl J Med 1987;317:185-91.
2. Fischl MA, Richman DD, Hansen N, et al. The safety and efficacy of zidovudine (AZT) in the treatment of mildly symptomatic human immunodeficiency virus type I (HIV) infection: a double-blind, placebo-controlled trial. Ann Intern Med 1990;112:727-37.
3. Volberding PA, Lagakos SW, Koch MA, et al. Zidovudine in asymptomatic human immunodeficiency virus infection: a controlled trial in persons with fewer than 500 CD4-positive cells per cubic millimeter. N Engl J Med 1990;322:941-9.
4. Friedland GH. Early treatment for HIV: the time has come. N Engl J Med 1990;322:1000-2.
5. Revision of the CDC surveillance case definition for acquired immunodeficiency syndrome. MMWR 1987;36:Suppl 1S:1S-15S.
6. Pocock SJ. Clinical trials: a practical approach. New York: John Wiley, 1983.
7. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-55.
8. Guidelines for prophylaxis against *Pneumocystis carinii* pneumonia for persons infected with human immunodeficiency virus. MMWR 1989;38:Suppl S-5:1-9.
9. Price RW, Brew BJ. The AIDS dementia complex. J Infect Dis 1988;158:1079-83.
10. Working Group of the American Academy of Neurology AIDS Task Force. Nomenclature and research case definitions for neurologic manifestations of human immunodeficiency virus-type I (HIV-1) infection. Neurology 1991;41:778-85.
11. Gitterman SR, Drusano GL, Egorin MJ, Standiford HC. Population pharmacokinetics of zidovudine. Clin Pharmacol Ther 1990;48:161-7.
12. Peto R, Pike MC, Armitage P, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. Analysis and examples. Br J Cancer 1977;35:1-39.
13. Kalbfleisch JD, Prentice RG. The statistical analysis of failure time data. New York: John Wiley, 1980.
14. Gail M, Simon R. Testing for qualitative interactions between treatment effects and patient subsets. Biometrics 1985;41:361-72.
15. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. Biometrics 1979;35:549-56.
16. Moore RD, Hidalgo J, Sugland BW, Chaisson RE. Zidovudine and the natural history of the acquired immunodeficiency syndrome. N Engl J Med 1991;324:1412-6.
17. Fischl MA, Parker CB, Pettinelli C, et al. A randomized controlled trial of a reduced daily dose of zidovudine in patients with the acquired immunodeficiency syndrome. N Engl J Med 1990;323:1009-14.
18. Richman DD, Fischl MA, Grieco MH, et al. The toxicity of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related complex: a double-blind, placebo-controlled trial. N Engl J Med 1987;317:192-7.